ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 03/10/2015

ClinicalTrials.gov ID: NCT00660907

Study Identification

Unique Protocol ID:	D1690C00004
Brief Title:	Efficacy and Safety of Dapagliflozin in Combination With Metformin in Type 2 Diabetes Patients
Official Title:	A 52-Week International, Multi-centre, Randomised, Parallel-group, Double-blind, Active-controlled, Phase III Study With a 156-Week Extension Period to Evaluate the Efficacy and Safety of Dapagliflozin in Combination With Metformin Compared With Sulphonylurea in Combination With Metformin in Adult Patients With Type 2 Diabetes Who Have Inadequate Glycaemic Control on Metformin Therapy Alone.
Secondary IDs:	

Study Status

Record Verification:	March 2015
Overall Status:	Completed
Study Start:	March 2008
Primary Completion:	December 2009 [Actual]
Study Completion:	January 2013 [Actual]

Sponsor/Collaborators

Sponsor:	AstraZeneca
Responsible Party:	Sponsor
Collaborators:	Bristol-Myers Squibb

Oversight

FDA Regulated?:	Yes
Applicable Trial?:	Section 801 Clinical Trial? Yes Delayed Posting? No
IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 10 December 2007 Board Name: Comité Independiente de Ética para Ensayos en Farmacología Clínica Board Affiliation: Comité Independiente de Ética para Ensayos en Farmacología Clínica Phone: 4952-3892 Email:
Data Monitoring?:	No
Plan to Share Data?:	
Oversight Authorities:	Argentina: Administracion Nacional de Medicamentos, Alimentos y Tecnologia Medica Brazil: National Health Surveillance Agency France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis) Germany: Federal Institute for Drugs and Medical Devices Italy: The Italian Medicines Agency Mexico: Federal Commission for Protection Against Health Risks Netherlands: The Central Committee on Research Involving Human Subjects (CCMO) South Africa: Medicines Control Council Spain: Spanish Agency of Medicines Sweden: Medical Products Agency United Kingdom: Medicines and Healthcare Products Regulatory Agency

Study Description

Brief Summary:	This study is being carried out to see if dapagliflozin as an addition to metformin is effective and safe in treating patients with type 2 diabetes when compared to glipizide (sulphonylurea) as an addition to metformin treatment.
Detailed Description:	

Conditions

Conditions:	Type 2 Diabetes
Keywords:	Dapagliflozin efficacy safety

metformin
Type 2 diabetes

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Intervention Model:	Parallel Assignment
Number of Arms:	2
Masking:	Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Allocation:	Randomized
Endpoint Classification:	Safety/Efficacy Study
Enrollment:	1217 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: 1 dapagliflozin plus metformin	Drug: dapagliflozin Tablet oral 2.5, 5, or 10 mg total daily dose once daily 208 weeks Drug: metformin hydrochloride Tablet oral 1500, 2000, or 2500 mg total daily dose split/twice daily 218 weeks Other Names: • Glucophage
Active Comparator: 2 glipizide plus metformin	Drug: glipizide Capsule oral 5, 10, or 20 mg total daily dose once or split/twice daily 208 weeks Other Names: • Glucotrol Drug: metformin hydrochloride Tablet oral 1500, 2000, or 2500 mg total daily dose split/twice daily 218 weeks Other Names: • Glucophage

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age: 150 Years

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Type 2 Diabetes
- Treated with oral anti-diabetic drug therapy therapy including Metformin for at least 8 weeks prior to enrolment
- HbA1c >6.5% and </=10%

Exclusion Criteria:

- Type 1 Diabetes
- Insulin therapy within one year of enrolment
- Renal (kidney) failure or dysfunction

Contacts/Locations

Study Officials: Michael A. Nauck, Prof. Dr. med.
Study Principal Investigator
Diabeteszentrum Bad Lauterberg, Germany

Locations: Argentina
Research Site
La Plata, Argentina

Research Site
Córdoba, Argentina

Research Site
Capital Federal, Argentina

Research Site
Buenos Aires, Argentina

Research Site

Rosario, Argentina

Research Site
Caba, Argentina

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Rosario, Argentina

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Buenos aires, Argentina

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Corrientes, Argentina

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Ciudad de Buenos Aires, Argentina

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Germany
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Bad Lauterberg, Germany

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Berlin, Germany

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Frankfurt, Germany

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München, Germany

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Ludwigshafen, Germany

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Wangen, Germany

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Schmiedeberg, Germany

Research Site
Pirna, Germany

Spain
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Cornellá de Llobregat (BCN), Spain

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Villar del Arzobispo(Valencia), Spain

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Alzira (Valencia), Spain

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Madrid, Spain

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Alicante, Spain

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Barcelona, Spain

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Sevilla, Spain

France
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Nantes Cedex 1, France

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Murs Erigne, France

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Tours, France

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Paris, France

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L'aigle, France

United Kingdom
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Addlestone, United Kingdom

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Coventry, United Kingdom

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Mortimer Reading, United Kingdom

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Ecclesfield, United Kingdom

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Newtownabbey, United Kingdom

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Netherlands
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Beek En Donk, Netherlands

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Wildervank, Netherlands

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Poortvliet, Netherlands

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Soerendonk, Netherlands

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Zutphen, Netherlands

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Gorinchem, Netherlands

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Driebergen, Netherlands

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Lichtenvoorde (gld), Netherlands

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Rotterdam, Netherlands

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Groningen, Netherlands

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Leiderdorp, Netherlands

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Södertälje, Sweden

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Cape Town, South Africa

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Umkomaas, South Africa

Research Site
Durban, South Africa

Research Site
Pretoria, South Africa

Research Site
Witbank, South Africa

Research Site
Pretoria, South Africa

Italy
Research Site
Chieti, Italy

References

Citations: [Study Results] Nauck MA, Del Prato S, Meier JJ, Durán-García S, Rohwedder K, Elze M, Parikh SJ. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care. 2011 Sep;34(9):2015-22. doi: 10.2337/dc11-0606. Epub 2011 Aug 4. PubMed 21816980

Links: URL: http://filehosting.pharmacm.com/DownloadService.ashx?client=CTR_MED_6111&studyid=289&fil...
Description CSR-D1690C00004.pdf

Study Data/Documents:

Participant Flow

Recruitment Details	The 1st patient was enrolled on 31 Mar 2008. The last patient last visit was on 15 Dec 2009. 1901 patients (pts) were screened and 1217 pts were enrolled with the aim to randomize 816. 2 randomized pts were excluded since they received no medication. Eventually, 814 pts received medication. This study was conducted at 95 centers world-wide.
Pre-Assignment Details	For participants with a metformin dose of less than 1500 mg/day, a change in metformin dose in the past 8 weeks or on an Oral Anti-Diabetic (OAD), an 8-week metformin-only dose stabilisation period occurred. A 2-week placebo lead in period occurred after the dose stabilisation period or after enrolment if dose stabilisation period was skipped.

Reporting Groups

	Description
Dapagliflozin Plus Metformin	Experimental dapagliflozin plus metformin
Glipizide Plus Metformin	Active Comparator glipizide plus metformin

Overall Study

	Dapagliflozin Plus Metformin	Glipizide Plus Metformin
Started	406 [1]	408 [2]
Completed	322	314
Not Completed	84	94
Incorrect Enrollment	1	1
Adverse Event	33	19
Subject No Longer Meets Study Criteria	6	27
Withdrawal by Subject	23	32
Lost to Follow-up	3	3
Poor/Non-Compliance	5	1
Safety	1	0
Death	1	3
Various	11	8

[1] Of the 406 randomized participants only 400 were included in the full analysis set.

[2] Of the 408 randomized participants only 401 were included in the full analysis set.

Baseline Characteristics

Analysis Population Description

Full Analysis Set defined as all randomized participants (as randomized) who received at least one dose of double-blind study medication, who have a non-missing baseline value and at least one post-baseline efficacy value for at least one efficacy variable during double-blind treatment period.

Reporting Groups

	Description
Dapagliflozin Plus Metformin	Experimental dapagliflozin plus metformin
Glipizide Plus Metformin	Active Comparator glipizide plus metformin

Baseline Measures

	Dapagliflozin Plus Metformin	Glipizide Plus Metformin	Total
Number of Participants	400	401	801
Age, Continuous [units: years] Mean (Standard Deviation)	58.1 (9.37)	58.6 (9.80)	58.4 (9.58)
Gender, Male/Female [units: Participants]			
Female	179	181	360
Male	221	220	441
Race/Ethnicity, Customized [units: Participants]			
American Indian or Alaska Native	0	0	0
Asian	27	34	61
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	26	24	50
White	327	323	650
More than one race	0	0	0
Unknown or Not Reported	20	20	40

	Dapagliflozin Plus Metformin	Glipizide Plus Metformin	Total
BMI [units: kg/m2] Mean (Standard Deviation)	31.71 (5.104)	31.23 (5.053)	31.47 (5.081)
HbA1c [units: percent] Mean (Standard Deviation)	7.69 (0.855)	7.74 (0.886)	7.72 (0.870)
FPG [units: ng/mL] Mean (Standard Deviation)	162.24 (37.796)	163.91 (41.559)	163.07 (39.708)

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Adjusted Mean Change in HbA1c Levels
Measure Description	To assess the effect of dapagliflozin plus metformin compared to glipizide plus metformin on the absolute change from baseline in HbA1c level after 52 weeks double-blind treatment in patients with type 2 diabetes who have inadequate glycaemic control on 1500 mg/day or higher doses of metformin therapy alone.
Time Frame	Baseline to Week 52
Safety Issue?	No

Analysis Population Description

Full Analysis Set, participants with non-missing baseline and Week 52 (LOCF) values

Reporting Groups

	Description
Dapagliflozin Plus Metformin	Experimental dapagliflozin plus metformin
Glipizide Plus Metformin	Active Comparator glipizide plus metformin

Measured Values

	Dapagliflozin Plus Metformin	Glipizide Plus Metformin
Number of Participants Analyzed	400	401
Adjusted Mean Change in HbA1c Levels [units: percent] Least Squares Mean (95% Confidence Interval)	-0.52 (-0.60 to -0.44)	-0.52 (-0.60 to -0.44)

Statistical Analysis 1 for Adjusted Mean Change in HbA1c Levels

Statistical Analysis Overview	Comparison Groups	Dapagliflozin Plus Metformin, Glipizide Plus Metformin
	Comments	The null hypothesis is given as H0: mean(treat) minus mean(reference) >= delta versus the alternative HA: mean(treat) minus mean(reference) < delta (with alpha = 0.025, one-sided)
	Non-Inferiority or Equivalence Analysis?	Yes
	Comments	non-inferior margin delta = 0.35

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	Significant at alpha=0.025 (1-sided). A hierarchical closed testing procedure was used to control Type I error across the primary & key secondary objectives
	Method	ANCOVA
	Comments	with treatment group as effect and baseline value as covariate

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	0.00
	Confidence Interval	(2-Sided) 95% -0.11 to 0.11
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.0569
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Adjusted Mean Change in Body Weight
Measure Description	To assess the effect of dapagliflozin plus metformin compared to glipizide plus metformin on body weight after 52 weeks double-blind treatment.
Time Frame	Baseline to Week 52
Safety Issue?	No

Analysis Population Description

Full Analysis Set, participants with non-missing baseline and Week 52 (LOCF) values

Reporting Groups

	Description
Dapagliflozin Plus Metformin	Experimental dapagliflozin plus metformin
Glipizide Plus Metformin	Active Comparator glipizide plus metformin

Measured Values

	Dapagliflozin Plus Metformin	Glipizide Plus Metformin
Number of Participants Analyzed	400	401
Adjusted Mean Change in Body Weight [units: kg] Least Squares Mean (95% Confidence Interval)	-3.22 (-3.56 to -2.87)	1.44 (1.09 to 1.78)

Statistical Analysis 1 for Adjusted Mean Change in Body Weight

Statistical Analysis Overview	Comparison Groups	Dapagliflozin Plus Metformin, Glipizide Plus Metformin
	Comments	H0: mean(treat) minus mean(reference) = 0 versus the alternative HA: mean(treat) minus mean(reference) =/= 0
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	Significant at alpha=0.05 (2-sided). Key secondary endpoints are tested following a hierarchical closed testing procedure
	Method	ANCOVA
	Comments	with treatment group as effect and baseline value as covariate

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-4.65
	Confidence Interval	(2-Sided) 95% -5.14 to -4.17
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.2483
	Estimation Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Proportion of Participants With at Least One Episode of Hypoglycemia
Measure Description	To assess the effect of dapagliflozin plus metformin treatment compared to glipizide plus metformin on the occurrence of hypoglycemic events. Least Squares Mean represents the percent of participants adjusted for HbA1c baseline value.
Time Frame	Baseline to Week 52
Safety Issue?	Yes

Analysis Population Description
Full analysis set

Reporting Groups

	Description
Dapagliflozin Plus Metformin	Experimental dapagliflozin plus metformin
Glipizide Plus Metformin	Active Comparator glipizide plus metformin

Measured Values

	Dapagliflozin Plus Metformin	Glipizide Plus Metformin
Number of Participants Analyzed	400	401
Proportion of Participants With at Least One Episode of Hypoglycemia [units: Percentage of participants] Least Squares Mean (95% Confidence Interval)	3.5 (1.7 to 5.3)	40.8 (36.1 to 45.5)

Statistical Analysis 1 for Proportion of Participants With at Least One Episode of Hypoglycemia

Statistical Analysis Overview	Comparison Groups	Dapagliflozin Plus Metformin, Glipizide Plus Metformin
	Comments	H0: proportion(treat) minus proportion(reference) = 0 versus the alternative HA: proportion(treat) minus proportion(reference) =/= 0
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	Significant at alpha=0.05 (2-sided). Key secondary endpoints are tested following a hierarchical closed testing procedure

	Method	Regression, Logistic
	Comments	Based on methodology of Zhang, Tsiatis & Davidian and Davidian, Tsiatis, Zhang & Lu, with adjustment for baseline value.

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	-37.2
	Confidence Interval	(2-Sided) 95% -42.3 to -32.2
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.578
	Estimation Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Proportion of Participants With Body Weight Reduction of at Least 5%
Measure Description	To evaluate the effect of dapagliflozin plus metformin compared to glipizide plus metformin on body weight assessed by a reduction after 52 weeks of at least 5% compared to baseline. Least Squares Mean represents the percent of participants adjusted for baseline value.
Time Frame	Baseline to Week 52
Safety Issue?	No

Analysis Population Description

Full Analysis Set, participants with non-missing baseline and Week 52 (LOCF) values

Reporting Groups

	Description
Dapagliflozin Plus Metformin	Experimental dapagliflozin plus metformin
Glipizide Plus Metformin	Active Comparator glipizide plus metformin

Measured Values

	Dapagliflozin Plus Metformin	Glipizide Plus Metformin
Number of Participants Analyzed	400	401
Proportion of Participants With Body Weight Reduction of at Least 5% [units: Percentage of participants] Least Squares Mean (95% Confidence Interval)	33.3 (28.7 to 37.9)	2.5 (1.0 to 4.0)

Statistical Analysis 1 for Proportion of Participants With Body Weight Reduction of at Least 5%

Statistical Analysis Overview	Comparison Groups	Dapagliflozin Plus Metformin, Glipizide Plus Metformin
	Comments	H0: proportion(treat) minus proportion(reference) = 0 versus the alternative HA: proportion(treat) minus proportion(reference) =/= 0
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	Significant at alpha=0.05 (2-sided). Key secondary endpoints are tested following a hierarchical closed testing procedure
	Method	Regression, Logistic
	Comments	Based on methodology of Zhang, Tsiatis & Davidian and Davidian, Tsiatis, Zhang & Lu, with adjustment for baseline value.

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	30.8
	Confidence Interval	(2-Sided) 95% 26.0 to 35.7
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.480
	Estimation Comments	[Not specified]

Reported Adverse Events

Time Frame	Non-serious / serious adverse events on or after the first day and on or prior to the last day of the 52-week double-blind treatment plus 4/30 days or up to follow-up visit if earlier, or up to and including the start date of extension period if earlier.
Additional Description	Participants were questioned at each study visit about the occurrence of any health problems and any examination conducted at a study visit was assessed in comparison to the status at study entry.

Reporting Groups

	Description
Dapagliflozin Plus Metformin	Experimental dapagliflozin plus metformin
Glipizide Plus Metformin	Active Comparator glipizide plus metformin

Serious Adverse Events

	Dapagliflozin Plus Metformin	Glipizide Plus Metformin
	Affected/At Risk (%)	Affected/At Risk (%)
Total	35/406 (8.62%)	46/408 (11.27%)
Blood and lymphatic system disorders		
Anaemia [A] †	0/406 (0%)	2/408 (0.49%)
Cardiac disorders		
Acute Coronary Syndrome [A] †	1/406 (0.25%)	0/408 (0%)
Acute Myocardial Infarction [A] †	0/406 (0%)	1/408 (0.25%)
Angina Pectoris [A] †	1/406 (0.25%)	1/408 (0.25%)
Atrial Fibrillation [A] †	1/406 (0.25%)	0/408 (0%)
Atrioventricular Block Complete [A] †	0/406 (0%)	1/408 (0.25%)
Bradycardia [A] †	0/406 (0%)	1/408 (0.25%)
Cardiac Arrest [A] †	1/406 (0.25%)	0/408 (0%)
Cardiac Failure [A] †	0/406 (0%)	1/408 (0.25%)
Cardiac Failure Congestive [A] †	0/406 (0%)	1/408 (0.25%)
Coronary Artery Disease [A] †	1/406 (0.25%)	1/408 (0.25%)
Left Ventricular Failure [A] †	1/406 (0.25%)	0/408 (0%)
Myocardial Infarction [A] †	1/406 (0.25%)	3/408 (0.74%)
Ventricular Arrhythmia [A] †	1/406 (0.25%)	0/408 (0%)
Eye disorders		

	Dapagliflozin Plus Metformin	Glipizide Plus Metformin
	Affected/At Risk (%)	Affected/At Risk (%)
Cataract [A] †	0/406 (0%)	1/408 (0.25%)
Retinal Detachment [A] †	1/406 (0.25%)	1/408 (0.25%)
Gastrointestinal disorders		
Abdominal Pain [A] †	0/406 (0%)	1/408 (0.25%)
Abdominal Pain Upper [A] †	1/406 (0.25%)	0/408 (0%)
Anal Fissure [A] †	0/406 (0%)	1/408 (0.25%)
Constipation [A] †	1/406 (0.25%)	0/408 (0%)
Dyspepsia [A] †	0/406 (0%)	1/408 (0.25%)
Gastritis [A] †	1/406 (0.25%)	0/408 (0%)
Haemorrhoids [A] †	1/406 (0.25%)	0/408 (0%)
Upper Gastrointestinal Haemorrhage [A] †	1/406 (0.25%)	0/408 (0%)
General disorders		
Chest Pain [A] †	0/406 (0%)	1/408 (0.25%)
Non-Cardiac Chest Pain [A] †	0/406 (0%)	1/408 (0.25%)
Sudden Death [A] †	0/406 (0%)	1/408 (0.25%)
Hepatobiliary disorders		
Cholecystitis [A] †	0/406 (0%)	1/408 (0.25%)
Cholecystitis Acute [A] †	0/406 (0%)	1/408 (0.25%)
Cholelithiasis [A] †	1/406 (0.25%)	0/408 (0%)
Hepatic Cirrhosis [A] †	1/406 (0.25%)	0/408 (0%)
Infections and infestations		
Bronchitis [A] †	1/406 (0.25%)	1/408 (0.25%)
Diverticulitis [A] †	0/406 (0%)	2/408 (0.49%)

	Dapagliflozin Plus Metformin	Glipizide Plus Metformin
	Affected/At Risk (%)	Affected/At Risk (%)
Erysipelas [A] †	0/406 (0%)	1/408 (0.25%)
Gastroenteritis [A] †	0/406 (0%)	1/408 (0.25%)
Gastroenteritis Viral [A] †	1/406 (0.25%)	0/408 (0%)
Liver Abscess [A] †	1/406 (0.25%)	0/408 (0%)
Lower Respiratory Tract Infection [A] †	1/406 (0.25%)	0/408 (0%)
Pneumonia [A] †	1/406 (0.25%)	1/408 (0.25%)
Pyelonephritis [A] †	0/406 (0%)	1/408 (0.25%)
Sepsis [A] †	1/406 (0.25%)	0/408 (0%)
Septic Shock [A] †	1/406 (0.25%)	0/408 (0%)
Injury, poisoning and procedural complications		
Ankle Fracture [A] †	1/406 (0.25%)	1/408 (0.25%)
Clavicle Fracture [A] †	0/406 (0%)	1/408 (0.25%)
Contusion [A] †	0/406 (0%)	1/408 (0.25%)
Humerus Fracture [A] †	0/406 (0%)	1/408 (0.25%)
Multiple Injuries [A] †	1/406 (0.25%)	0/408 (0%)
Overdose [A] †	0/406 (0%)	2/408 (0.49%)
Postoperative Renal Failure [A] †	0/406 (0%)	1/408 (0.25%)
Road Traffic Accident [A] †	0/406 (0%)	1/408 (0.25%)
Wrist Fracture [A] †	0/406 (0%)	1/408 (0.25%)
Investigations		
Creatinine Renal Clearance Decreased [A] †	1/406 (0.25%)	0/408 (0%)
Metabolism and nutrition disorders		

	Dapagliflozin Plus Metformin	Glipizide Plus Metformin
	Affected/At Risk (%)	Affected/At Risk (%)
Hypoglycaemia [A] †	0/406 (0%)	3/408 (0.74%)
Hyponatraemia [A] †	1/406 (0.25%)	0/408 (0%)
Musculoskeletal and connective tissue disorders		
Arthralgia [A] †	0/406 (0%)	1/408 (0.25%)
Intervertebral Disc Protrusion [A] †	0/406 (0%)	1/408 (0.25%)
Rotator Cuff Syndrome [A] †	0/406 (0%)	1/408 (0.25%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Basal Cell Carcinoma [A] †	0/406 (0%)	1/408 (0.25%)
Breast Cancer [A] †	1/406 (0.25%)	0/408 (0%)
Bronchial Carcinoma [A] †	0/406 (0%)	1/408 (0.25%)
Prostate Cancer [A] †	3/406 (0.74%)	1/408 (0.25%)
Nervous system disorders		
Carotid Artery Stenosis [A] †	1/406 (0.25%)	0/408 (0%)
Cerebral Thrombosis [A] †	1/406 (0.25%)	0/408 (0%)
Cervicobrachial Syndrome [A] †	1/406 (0.25%)	0/408 (0%)
Loss Of Consciousness [A] †	1/406 (0.25%)	0/408 (0%)
Migraine [A] †	0/406 (0%)	1/408 (0.25%)
Transient Ischaemic Attack [A] †	1/406 (0.25%)	0/408 (0%)
Psychiatric disorders		
Depression Suicidal [A] †	0/406 (0%)	1/408 (0.25%)
Obsessive-Compulsive Disorder [A] †	0/406 (0%)	1/408 (0.25%)
Renal and urinary disorders		
Diabetic Nephropathy [A] †	1/406 (0.25%)	0/408 (0%)

	Dapagliflozin Plus Metformin	Glipizide Plus Metformin
	Affected/At Risk (%)	Affected/At Risk (%)
Nephrolithiasis [A] †	0/406 (0%)	1/408 (0.25%)
Urinary Incontinence [A] †	0/406 (0%)	1/408 (0.25%)
Reproductive system and breast disorders		
Uterine Prolapse [A] †	2/406 (0.49%)	0/408 (0%)
Respiratory, thoracic and mediastinal disorders		
Alveolitis Allergic [A] †	1/406 (0.25%)	0/408 (0%)
Asthma [A] †	0/406 (0%)	1/408 (0.25%)
Pulmonary Embolism [A] †	1/406 (0.25%)	0/408 (0%)
Skin and subcutaneous tissue disorders		
Angioedema [A] †	1/406 (0.25%)	0/408 (0%)
Urticaria [A] †	1/406 (0.25%)	0/408 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 12.1

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Dapagliflozin Plus Metformin	Glipizide Plus Metformin
	Affected/At Risk (%)	Affected/At Risk (%)
Total	163/406 (40.15%)	260/408 (63.73%)
Endocrine disorders		
Hypoglycemia [A] †	14/406 (3.45%)	162/408 (39.71%)
Gastrointestinal disorders		
Diarrhoea [A] †	19/406 (4.68%)	26/408 (6.37%)
Infections and infestations		
Influenza [A] †	30/406 (7.39%)	30/408 (7.35%)

	Dapagliflozin Plus Metformin	Glipizide Plus Metformin
	Affected/At Risk (%)	Affected/At Risk (%)
Nasopharyngitis [A] †	43/406 (10.59%)	61/408 (14.95%)
Upper Respiratory Tract Infection [A] †	24/406 (5.91%)	31/408 (7.6%)
Urinary Tract Infection [A] †	30/406 (7.39%)	17/408 (4.17%)
Musculoskeletal and connective tissue disorders		
Arthralgia [A] †	11/406 (2.71%)	21/408 (5.15%)
Nervous system disorders		
Dizziness [A] †	15/406 (3.69%)	37/408 (9.07%)
Headache [A] †	21/406 (5.17%)	17/408 (4.17%)
Tremor [A] †	1/406 (0.25%)	31/408 (7.6%)
Skin and subcutaneous tissue disorders		
Hyperhidrosis [A] †	5/406 (1.23%)	27/408 (6.62%)
Vascular disorders		
Hypertension [A] †	30/406 (7.39%)	35/408 (8.58%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 12.1

Limitations and Caveats

For participants who did not complete 52 weeks LOCF (last observation carried forward) was used.

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

If an Investigator requests permission to publish data from this study any such publication is to be agreed with AstraZeneca (AZ) in advance. The investigator agrees to provide AZ as soon as possible with drafts of proposed publications. Unless otherwise agreed, AZ shall have a period of 60 days

from receipt of the proposed final manuscript to review it and may within such time require that submission for publication of the manuscript be delayed in order for AZ to file patent applications.

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